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Utilizing stochastic genetic epidemiological models to quantify the impact of selection for resistance to infectious diseases in domestic livestock[1]

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ABSTRACT: This paper demonstrates the use of stochastic genetic epidemiological models for quantifying the consequences of selecting animals for resistance to a microparasitic infectious disease. The model is relevant for many classes of infectious diseases where sporadic epidemics occur, and it is a powerful tool for investigating the costs, benefits, and risks associated with breeding for resistance to specific diseases. The model is parameterized for transmissible gastroenteritis, a viral disease affecting pigs, and selection for resistance to this disease on a structured pig farm is simulated. Two genetic models are used, both of which involve selection of sires. The first involves selection with the assumption of continuous genetic variation (the continuous selection model). The second involves selection with the assumption of introgression of a major recessive gene that confers resistance (the gene introgression model). In the base population, the basic reproductive ratio, R_0 (i.e., the expected number of secondary cases after the introduction of a single infected animal) was 2.24, in agreement with previous studies. The probabilities of no epidemic, a minor epidemic (one that dies out without intervention), and a major epidemic were 0.55, 0.20, and 0.25, respectively. Selection for resistance, under both genetic models, resulted in a nonlinear decline in the probability of a major epidemic and a decrease in the severity of the epidemic, should it occur, until R_0 was less than 1.0, at which point the probability of a major epidemic was zero. For minor epidemics, the probability and severity of the epidemic increased until R_0 reached 1.0, at which point the probabilities also fell to zero. The epidemic probabilities were critically dependent on the location on the farm where infected animals were situated, and the relative risks of different groups of animals changed with selection. The main difference between the two genetic models was in the time scale; the introgression results simply depended on how quickly the resistance allele could be introgressed into the population. For the introgression model, the probability of a major epidemic declined to zero when 0.6 of the animals were homozygous for the resistance allele.

Key Words: Disease Resistance, Epidemiology, Pigs, Selection, Stochastic Models

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Introduction

Genetic selection of resistant animals is increasingly looked upon as a means of combating infectious diseases in domestic livestock; for many diseases, there is substantial evidence that resistance has a genetic component. For example, estimates of heritabilities for traits involved in disease resistance generally range from 0.1 to 0.4 (Sacco et al., 1994; Morris, 1998), similar to heritabilities for production traits. Selection experiments have shown that it is possible to exploit these genetic differences in resistance (Afraz et al., 1994; Mallard et al., 1998; Morris, 1998). Finally, genes or quantitative trait loci influencing disease resistance have been demonstrated (Belt et al., 1995; Edfors-Lilja et al., 1995).

Genetic selection for resistance to infectious diseases, although possible, may be difficult and costly. Therefore, it is imperative that an assessment of the costs, benefits, and consequences be performed prior to selection. For example, will selection for resistance to a specific disease reduce disease incidence or severity to an acceptable level within a reasonable time period? These questions can only be answered if the interactions between host genotype and disease epidemiology are fully understood. In turn, this requires epidemic models that include host genotype for resistance.

MacKenzie and Bishop (2001) described a stochastic epidemic model for predicting the consequences of microparasitic (e.g., viral) disease epidemics in structured livestock populations. In this paper, the model of MacKenzie and Bishop (2001) is adapted to include host genotype, in order to assess the impact of selecting hosts that are resistant to specific microparasitic diseases on

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the risks posed by that disease. The model is parameterized using transmissible gastroenteritis (**TGE**), a pig disease previously modeled by Hone (1994). This disease was selected because the parameters for the model have already been estimated, allowing the results to be compared to published data.

Materials and Methods

Epidemic Model and Farm Structure

The basic stochastic epidemic model used in this paper is outlined by MacKenzie and Bishop (2001). In brief, a stochastic epidemic model simulates the epidemic process as a series of random events in time and space, with the probability of specific events defined by the parameters of the model. The two components of the model are the inter-event time, which is drawn from an exponential distribution, and the event type. In the simple model of MacKenzie and Bishop (2001), two parameters were considered, the transmission coefficient and the recovery rate. The transmission coefficient is the rate at which new infections occur and is the expected number of new infections per infectious animal per susceptible animal per unit of time. Transmission is assumed to take place directly between susceptible and infected animals. The recovery rate is the inverse of the infectious period and is the expected number of recoveries per infectious animal per unit of time. The possible events were either an animal recovering or the animal infecting another. The probabilities of these events are then modified according to the farm structure, which dictates the contact rates between different classes of animals and thus the range of events that can actually take place and their respective probabilities.

Application of this model to specific diseases requires addition of parameters describing the biology of each particular disease, although the basic methodology remains the same. For TGE in pigs these include the latent period, the disease-dependent mortality (which is age-dependent), and the rate of loss of immunity in recovered pigs. Hone (1994) has previously estimated these parameters and these estimates are as follows: transmission coefficient = 0.0007/d, recovery rate = 0.057/d, and latent period = 2 d; thus, the rate at which latent pigs become infectious = 0.5/d, mortality rate = 0.006/d for pigs over 4 wk of age and 0.1712/d for piglets 4 wk of age or less, and the rate of loss of immunity = 0.0031/d. The model is further extended to allow each type of pig to have a different value for the transmission coefficient, thus allowing incorporation of host genetic effects in this parameter. In this particular model, the recovery rate is assumed to be constant across all types, as are the latent period and rate of loss of immunity, although the disease-dependent mortality varies (nongenetically) according to animal type. The possible event types for this model are the following: a susceptible animal becomes latently infected, a latently infected animal become infectious, an infected animal recovers or dies as a result of infection, or an animal that has recovered loses immunity.

For a population with Y infected animals, X susceptible animals, L animals in the latent class, and Q recovered animals, the inter-event time in a TGE epidemic has a mean

$$1/\left(\gamma\sum_{i=1}^{n}Y_i+\sum_{i=1}^{n}Y_i\varepsilon_i+\sum_{i=1}^{n}\sum_{j=1}^{n}\beta_j c_{ji}Y_iX_j+\sigma\sum_{i=1}^{n}L_i+\omega\sum_{i=1}^{n}Q_i\right) \quad [1]$$

where γ is the recovery rate, β_j is the transmission coefficient for a pig of type j, and c_{ji} is the contact rate between type j and type i pigs, ε_i is the disease-dependent mortality rate for a pig of type i, ω is the rate of loss of immunity, and σ is the rate at which latent pigs become infectious. Thus, the inter-event time is drawn from an exponential distribution as $-\ln(r) \times$ (mean inter-event time), where r is a random number in [0,1].

The event type probabilities are calculated as follows. The sum $\sum_{i=1}^{n}\sum_{j=1}^{n}(Y_j(\beta_iX_ic_{ji}+\gamma_j+\varepsilon_j)+\sigma L_i+\omega Q_i)$ is calculated and is denoted by RATE. The probability that the next event is the infection of a pig of type i by a pig of type j, moving that pig to the latent class, is given by

$$\beta_iX_iY_j\,c_{ji}/\text{RATE} \quad [2]$$

for all i, j. The probability that it is the movement of a latent pig to the infectious class is given by

$$\sigma L_i/\text{RATE} \quad [3]$$

for all i and the probability that the next event is recovery of a type j animal is

$$\gamma Y_j/\text{RATE} \quad [4]$$

for all j. The probability that the next event is the death of a type j pig is

$$\varepsilon_jY_j/\text{RATE} \quad [5]$$

for all j and the probability that it is the loss of immunity of a previously infected pig is

$$\omega Q_i/\text{RATE} \quad [6]$$

for all i.

Having obtained these probabilities, a random number, r, is generated. The probability given by Eq. [2] is compared with this random number, and if r is less than this probability, then the event type is the infection of an animal of type i by an animal of type j, moving the type i animal to the latent class. Otherwise, r is compared to the sum of the probabilities given in Eq.

[2] and [3]. If r is less than this sum, then the next event is the movement of an animal from the latent class to the infectious class. This process is repeated until an event has been defined.

The farm structure used is a closed farrow-to-finish pig farm, described in MacKenzie and Bishop (2001). On this farm, animals are classified into 54 type-age categories on a weekly basis, according to their age and physiological status.

Incorporating Genetics

Defining the Base Population. The population of pigs was assumed to have genetic variability in the transmission coefficient, β, which may be thought of as a composite of susceptibility and infectivity. The base population was generated such that each animal had a transmission coefficient phenotype made up of a genetic component, an environmental component, and a maternal component. The mean genetic component is constant across types in the base population, although it could be type-dependent, and is drawn from a normal distribution with SD dependent on the heritability of the trait, h^2, and the coefficient of variation for the population. Thus, if the phenotypic standard deviation is SD then the genetic standard deviation is $\sqrt{(h^2)} \times$ SD. The maternal and environmental components are drawn from a normal distribution with mean zero and standard deviation $\sqrt{(m^2)} \times$ SD and $\sqrt{(1 - m^2 - h^2)} \times$ SD respectively, where m^2 is the maternal effect. For simplicity, the maternal component is considered to be constant for all types and ages of pigs. If the resulting phenotypic value for any animal is less than zero, then it is reset to zero.

The assumed genetic parameters for the transmission coefficient of the base population are as follows: mean genotype = 0.0007, heritability (h^2) = 0.3, coefficient of variation (CV) = 0.75, maternal variance component (m^2) = 0.1, environmental variance component = 0.6. The coefficient of variation was set to 0.75 to reflect the variability often seen in measurements associated with disease resistance (e.g., Stear et al., 1995; Bishop et al., 1996).

Selection for Resistance, Assuming Continuous Genetic Variation. Hereinafter this model will be called the continuous selection model. Genetic improvement in the transmission coefficient is assumed to be at a constant rate ΔG and is achieved by the use of sires selected for resistance to this disease (e.g., using genetic markers or indicator traits). These sires are assumed to come from a separate population (e.g., the nucleus of a breeding company). In the nucleus the expected relative response to selection is $h^2 \times CV \times [i/L]$, where i is the selection intensity and L is the generation interval. Reasonable values for i and L are 0.4 and 2.2 yr, respectively, corresponding to our assumed rate of improvement, ΔG, of 4% of the initial value per annum. The consequences of the Bulmer effect (Falconer and Mackay, 1996), that is, the reduction in variance and heritability caused by selection, are not considered.

Initially, genetic improvement on the farm is only through the sires, but when gilts reared on the farm are used to replace sows, improvement comes from both the sire and the dam. The gilts are randomly selected from the finishing pigs. Thus, given an initial value of the transmission coefficient, β_{initial}, the next cohort of sires, β_{new}, have expected levels given by

$$\beta_{new} = \beta_{current} - \Delta G_t \beta_{initial} \quad [7]$$

where $\beta_{current}$ is the current level in the population for the transmission coefficient and ΔG_t is the increment in improvement, expressed as a proportion, for the relevant time period t. Sire genotypes are therefore drawn from a normal distribution with mean given in Eq. [7] and genetic standard deviation $\sqrt{(h^2)} \times$ SD, where SD is the sire population mean multiplied by the coefficient of variation. Piglet genotypes are given by $\frac{1}{2}(\beta g_{sire} + \beta g_{dam})$ + Mendelian sampling term, where βg_{sire} is the genetic component of the sire transmission coefficient, βg_{dam} is the genetic component of the dam transmission coefficient, and the Mendelian sampling term is drawn from a distribution with a mean of zero and genetic standard deviation $\sqrt{(0.5\ h^2)} \times$ SD. The farm population mean multiplied by the coefficient of variation is used for the SD. All piglets born to a common dam have a common maternal component. The estimate for β used to simulate epidemics is the mean transmission coefficient of each type rather than the individual values.

Selection for Resistance, Assuming Introgression of a Major Gene. Hereinafter this model will be called the gene introgression model. In this implementation of the model resistance is achieved by introgressing a major recessive resistance gene. The base population genetic structure is the same as that used for the continuous selection model. It is assumed that the farm population is homozygous for the dominant susceptibility gene but that sires are selected from a population homozygous for the resistance gene. Pigs on the farm have transmission coefficient β until they have two copies of the resistance gene when β is set to an arbitrary, low level (i.e., $<<1$). Again, the estimate for β used to simulate epidemics is the mean transmission coefficient of each type rather than the individual values. It is assumed that a sow with one copy of the resistance gene will pass that gene on to the piglets with probability of ½; thus, piglet genotypes are randomly sampled from a binomial distribution with $P = 0.5$.

Simulation Procedure

Selection for resistance was simulated on the pig farm using both the continuous selection and gene introgression models. In the base population, and every 52 wk for the continuous selection model, and every 5 wk for the gene introgression model, epidemics were simulated by introducing the pathogen onto the farm (i.e.,

Table 1. Results of stochastic transmissible gastroenteritis model for the base population

Parameter	No epidemic	Minor epidemic	Major epidemic
Probability	0.55	0.20	0.25
Probability SE	0.002	0.004	0.004
Maximum number of infections	1	4	18,110
Total proportion infected during epidemic	0	0.00053	0.65
Maximum proportion infected at one time	0	0.00038	0.13

by creating index cases). At each time point R_0 was estimated using the method of MacKenzie and Bishop (2001). After R_0 reached a value of 0.1, the selection process was stopped, because the probability of there being no epidemic is close to unity at this point. The results presented for both selection methods are based on the results of 10 simulated base populations. Furthermore, for each base population and at each time point, 10 simulations (index cases) were performed for each of the 54 types of pig, making a total of 5,400 simulations at each time point. The results presented for the probability of an epidemic and the probability that there is no epidemic, a minor epidemic, or a major epidemic are the means of the 5,400 simulations. For R_0, the results are the mean of 10 estimates, each comprising 540 simulations.

The methodology described in MacKenzie and Bishop (2001) was used to estimate the probability of an epidemic after the introduction of TGE by an index case. Epidemics that lasted for 1 yr were deemed to be major epidemics and the process was stopped.

The total (I) and maximum (y_{max}) proportions of pigs infected during each epidemic were obtained directly from simulation. The total proportion is calculated by counting the total number of pigs infected and dividing that total by the total number of susceptible pigs on the farm during the simulation. The maximum proportion infected at any one time is obtained by calculating the proportion of animals infected at each stage of the epidemic. Because the model is implemented to run for a maximum of 1 yr, the estimates based on the model are underestimates of the equilibrium values for these parameters. The standard error of the estimate of R_0 was determined using the methodology of MacKenzie and Bishop (2001).

Results

Base Population Results

When the base population was exposed to transmissible gastroenteritis, R_0 was estimated to be 2.24 (SE = 0.2). The total and maximum proportions of pigs infected during an epidemic, based on R_0 using Eq. [4] and [5] of Mackenzie and Bishop (2001), were 0.85 and 0.19, respectively. Table 1 summarizes the results for the base population.

The SE for the estimates of the probability of an epidemic are small, reflecting the precision of the simulation procedures in estimating these probabilities. The values given for the total and maximum proportion of pigs infected during a minor epidemic are the average total and maximum proportions of the population that became infected before the epidemic died out and are included to demonstrate that a minor epidemic may well go unnoticed. The total proportion of pigs infected by the index case during minor epidemics of 0.00053 corresponds to three pigs. In 75% of simulations, the introduction of an infected pig will have no major consequence.

Continuous Selection Model

The population transmission coefficient decreased at the expected rate, approximately 4%/yr, but was lagged by the time taken for the improved piglets, themselves, to give birth. Figure 1 shows effect of selection for resistance to transmissible gastroenteritis on R_0 and the probability of no epidemic or minor or major epidemics as selection proceeds. Each point on the figure represents the average probabilities of no epidemic, a minor

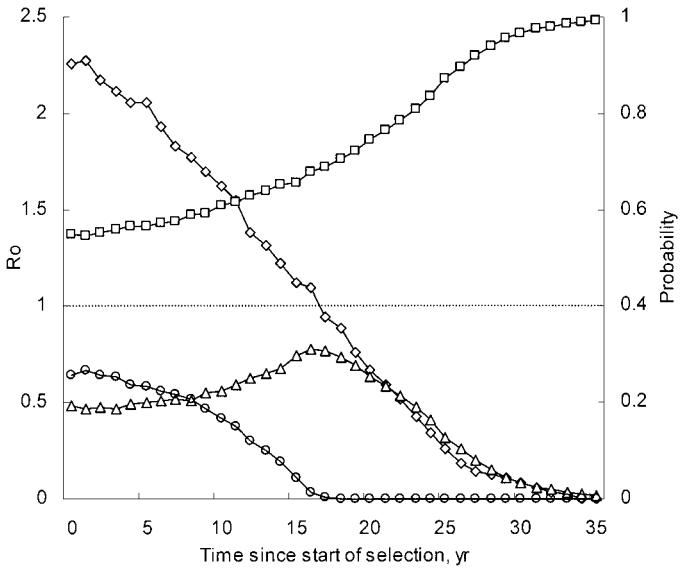


Figure 1. Effect of selection for resistance to transmissible gastroenteritis on the basic reproductive ratio (R_0) (◇) and the probability of no epidemic (□), a minor epidemic (△), or a major epidemic (○) at each time point under the continuous selection model. Dashed line denotes R_0 = 1. Each point is estimated from 5,400 simulations.

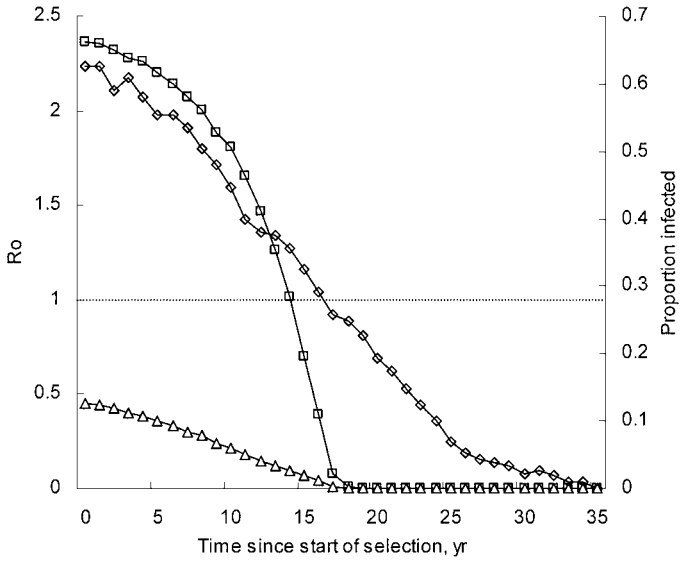


Figure 2. Effect of selection for resistance to transmissible gastroenteritis on the basic reproductive ratio (R_0) (◇), the total proportion (□), and the maximum proportion (△) of animals infected during major epidemics at each time point under the continuous selection model. Dashed line denotes $R_0 = 1$. Each point is estimated from 5,400 simulations.

epidemic, or a major epidemic and R_0 over all simulations at that point in time. The figure shows that rate of the reduction in R_0 begins to tail off after selection has reduced R_0 below 1.0 because of the reduction in variance in the transmission coefficient as it approaches zero. The variability in R_0 was greater at the start of selection (result not shown). As selection proceeds the variance of the transmission coefficient, which is proportional to the current mean, decreases, resulting in reduced variability in the simulations. Within 2 yr of the start of the selection process the probability that there will be no epidemic upon introduction of infection starts to increase and the probability that there will be a major epidemic decreases. However, until R_0 falls below 1, the probability that there will be a minor epidemic increases. This is because the population is less susceptible and can tolerate an increase in the number of infectious pigs before a major epidemic occurs. Thus, as selection proceeds, the number of minor epidemics will initially increase. After selection for reduced transmission coefficient has produced a population in which R_0 is less than 1 the probability of a major epidemic falls to zero. However, minor epidemics can still occur.

Figure 2 shows the mean estimates for the total (I) and maximum (y_{max}) proportions of pigs infected during the course of an epidemic as selection proceeds. The mean for R_0 is included in the figure for illustration. Again, each point on the graph represents the average total (I) or maximum (y_{max}) proportion of pigs infected after the introduction of an index case at that point in time. Only major epidemics were used to estimate the total and maximum proportions of pigs infected, and these were stopped after 1 yr.

Figure 3 shows the values for total and maximum proportion of pigs infected during minor epidemics. At no point do more than 1% of pigs become infected during a minor epidemic. Initially the proportion of pigs infected is less than 0.001, representing approximately six pigs, but as selection proceeds this increases to a maximum of 0.008, or about 50 pigs. Even when R_0 is less than 1, a small number of pigs still become infected. When R_0 is greater than 1, a reduction in the maximum and total proportion of pigs infected in major epidemics corresponds to an increase in the proportions infected in minor epidemics. This is because the reduced susceptibility of pigs allows a greater number of infected pigs to be present before a minor epidemic becomes a major epidemic. That is, the force of infection has to be greater for pigs of reduced susceptibility before a major epidemic can occur. In summary, as R_0 approaches 1.0, both the probability and severity of minor epidemics increases, but as R_0 falls below 1.0, both entities decrease.

The consequence of introducing an infectious pig onto the farm depends on the type of the pig. Figure 4 shows the probability of (a) major epidemics and (b) minor epidemics by index case type. Figure 4a shows that the probability of an epidemic is greater for classes of pigs containing large numbers of animals. As selection proceeds the probability falls for all classes, reaching zero after approximately 15 yr. As a class, the pigs with the greatest likelihood of causing an epidemic are the

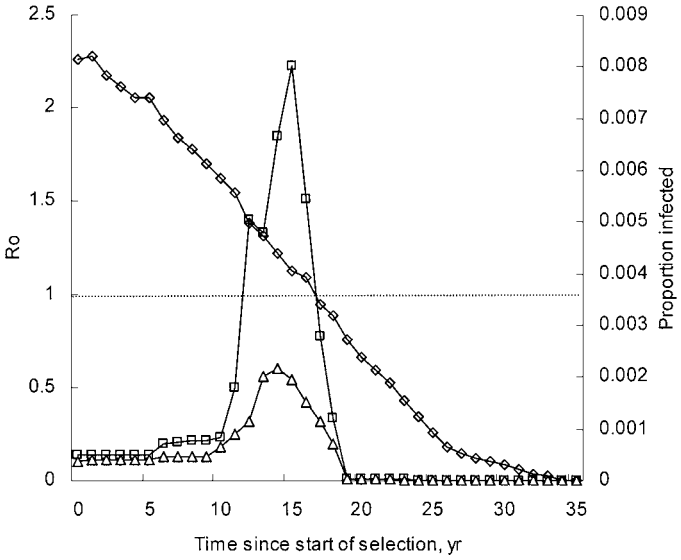
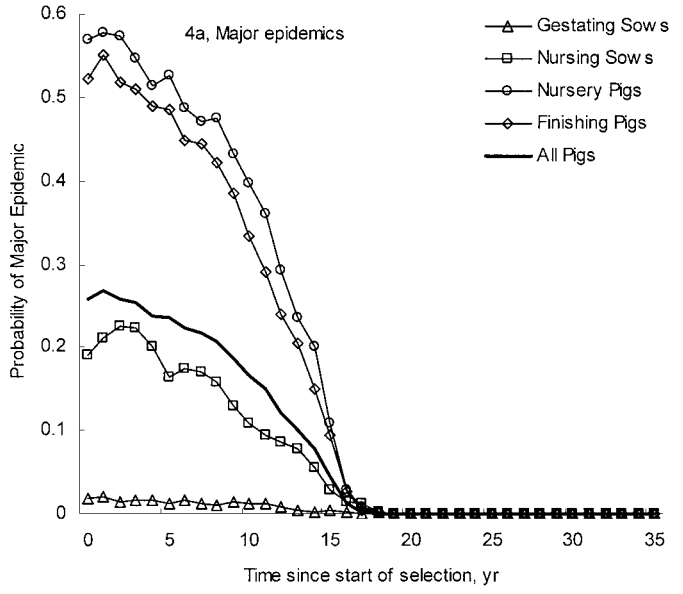


Figure 3. Effect of selection for resistance to transmissible gastroenteritis on the basic reproductive ratio, (R_0) (◇), the total proportion (□), and the maximum proportion (△) of animals infected during minor epidemics at each time point under the continuous selection model. Dashed line denotes $R_0 = 1$. Each point is estimated from 5,400 simulations.

nursery pigs, and this situation persists throughout the selection process. Less than 2% of simulations in which the index case is a mating sow or a gilt resulted in a major epidemic. These classes each contain less than 30 pigs. Figure 4b shows that with regard to minor epidemics, the relative rankings of the different types change under selection. Initially, the class most likely to cause a minor epidemic is the gestating sows. This is a small class with the potential to infect piglets. However, if these infected piglets have recovered before they are weaned, then the epidemic will die out, resulting in a minor rather than a major epidemic. As selection proceeds, the larger classes, with reduced susceptibility, now cause the majority of the minor epidemics. As stated above, this is because the reduction in susceptibility of the pigs means that a greater number of infected animals need to be present before a major epidemic can occur.



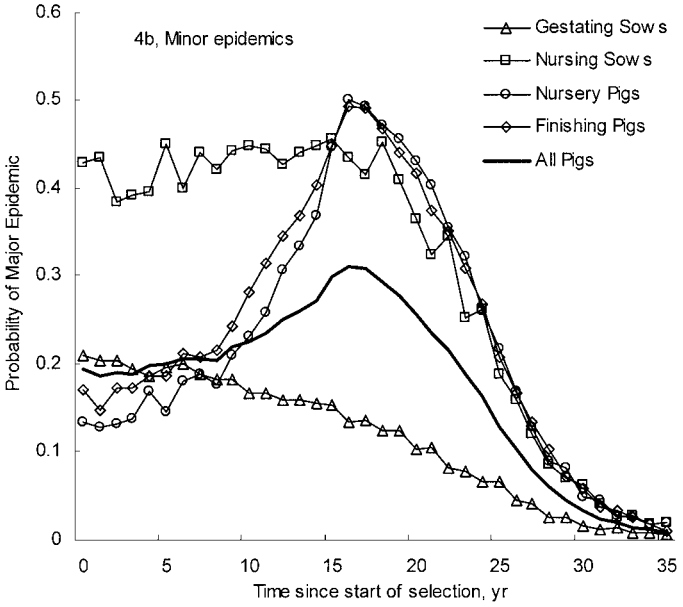


Figure 4. The probability of (a) major epidemics and (b) minor epidemics by index case type (heavy black line indicates mean for all pigs), during selection for resistance to transmissible gastroenteritis, under the continuous selection model. Each point is estimated from 5,400 simulations.

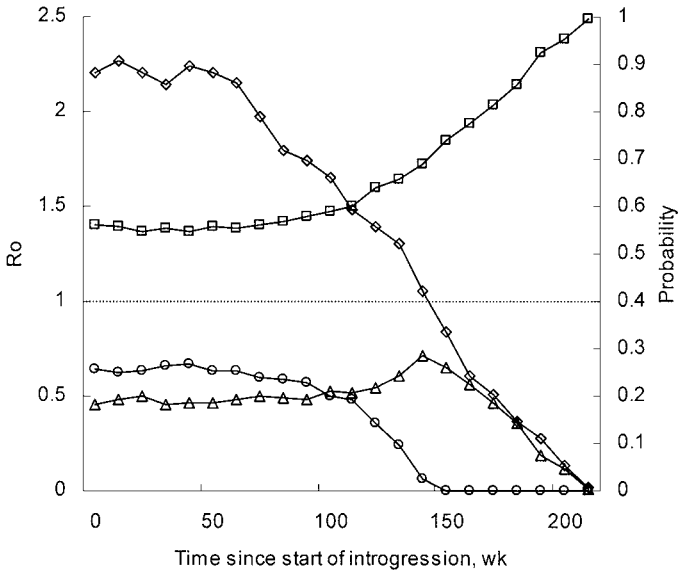


Figure 5. Effect of introgression of a recessive allele conferring resistance to transmissible gastroenteritis on the basic reproductive ratio, (R_0) (◇) and the probability of no epidemic (□), a minor epidemic (△), or a major epidemic (○) at each time point. Dashed line denotes $R_0 = 1$. Each point is estimated from 5,400 simulations.

Gene Introgression Model

The changes in gene and homozygote frequencies as introgression proceeds are the same as those produced by the discrete-time model of MacKenzie and Bishop (1999). The first signs of reduction in the transmission coefficient occur after 68 wk, when the first piglets carrying one copy of the allele give birth to resistant piglets with two copies of the allele. The reduction is not large, because the replacement rate for sows is 45% per annum, corresponding to around four sows per week. From these sows, approximately 50% of the piglets will be resistant (i.e., about 22 piglets out of 231). As more and more sows are replaced with piglets possessing the resistance allele, a greater number of resistant piglets are born. The population transmission coefficient reaches that of the sires after approximately 200 wk.

The epidemiological parameters for the base population were very similar to those described for continuous selection. Initially $R_0 = 2.36$ (SE = 0.2). Figure 5 shows the mean values for the basic reproductive rate and the probability that the introduction of an infected animal will cause no epidemic, a minor epidemic, or a major epidemic, with R_0 included for comparison. The results

are very similar to those obtained in the continuous selection program apart from the time-scale. Under this implementation, the population will be free from the risk of major epidemics after approximately 3 yr, but not free from the risk of minor epidemics until the introgression process is complete. It can be seen that the probability of a major epidemic reaches zero before the gene frequency reaches unity (i.e., it is not necessary to take the allele to fixation to render the population safe from major epidemics). For transmissible gastroenteritis, the proportion of animals that need to be resistant for the population to be free from major epidemics is 0.6 for the farm structure modeled.

Figure 6 presents the results for the total and maximum proportions of pigs infected, should an epidemic occur, again with R_0 shown for comparison. The response in the proportion of pigs infected is very similar in shape to that seen when continuous selection was applied, with only the time-scale being substantially different.

Discussion

A stochastic genetic epidemiological model has been developed that illustrates the consequences of selecting animals for resistance to an infectious microparasitic disease. This model has been parameterized for transmissible gastroenteritis in pigs, although it could equally well have been parameterized for a different infection or a different host species. The model has been developed in the context of selection assuming both continuous genetic variation and introgression of a recessive allele conferring resistance. The model produces an abundance of information about the way in which selection for resistance influences the probabilities or risks of epidemics, and the severity of these epidemics, should they occur. Additionally, the groups of animals most at risk and the effect of the location where the epidemic strikes on the farm can be quantified.

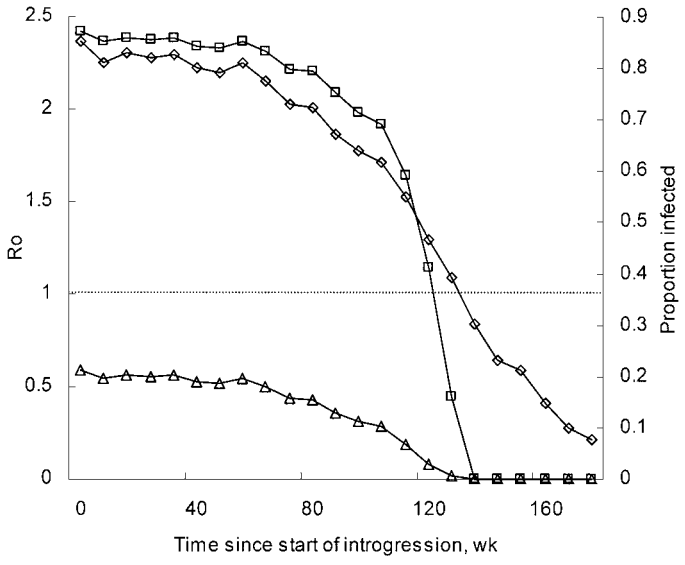


Figure 6. The basic reproductive ratio (R_0) (◇), and the total (□) and maximum (△) proportions of pigs infected during an epidemic at each time point during the introgression of an allele conferring resistance to transmissible gastroenteritis. Dashed line denotes $R_0 = 1$. Each point is estimated from 5,400 simulations.

The first question to be addressed is how well our model actually predicts the dynamics of TGE under field conditions. Pritchard (1987) reported that in 53% of herds with more than 250 sows, TGE is likely to become endemic. These endemic scenarios were frequently associated with herds that retained finishing pigs. This finding corresponds well with the results for the base population, in which 56% of epidemics become endemic. To quantify the disease dynamics, the model assumes that there is no intervention by the farmer in the event of an epidemic. Under this assumption, the baseline result for the basic reproductive ratio, R_0, for TGE is in good agreement with the estimate obtained by Hone (1994) of 2.0 for a breeding farm and 4.0 for a finishing farm. The result of 2.24 obtained by the current models of a farrow-to-finish farm lies within these values.

Several general results emerged from this study that are applicable not only to TGE, but also to other microparasitic diseases causing sporadic epidemics. First, given genetic change in the transmission coefficient, the probability of a major epidemic declines in a nonlinear manner as selection proceeds, as does the severity of the epidemic, should it occur. In agreement with theory, the probability of a major epidemic goes to zero as R_0 declines below 1.0. The probability of a minor epidemic, one that dies out without intervention, increases as R_0 approaches 1.0, as does the severity of the minor epidemic; however, as R_0 declines below 1.0, both the probability and severity of the minor epidemic decline to zero. The increase in the probability of a minor epidemic is caused by the failure of potential epidemics to become major as the transmission coefficient decreases.

The major difference between the continuous selection model and the gene introgression model is in the time-scale of events. The changes in the probabilities are qualitatively similar. In agreement with the results of Mackenzie and Bishop (1999), with their simpler discrete-time model, it is not necessary to take the gene to fixation in a gene introgression program to free the population from the risk of major epidemics. In this example and for this farm structure, the probability of a major epidemic is zero when 0.6 of the pigs are homozygous for the resistance allele.

A crucial result from this paper is that the probability of an epidemic is dependent on the index case type (i.e., where on the farm the disease strikes). If the index case is a nursery pig, then the probability that this animal causes an epidemic will be higher than 0.5 (Figure 6a), whereas if the index case is a gestating sow this probability is close to zero. Additionally, the relative probabilities of an epidemic associated with the different pig

types vary as selection proceeds. Although the relative ranking of different pig types, in terms of probabilities of major epidemics, remains similar as selection proceeds, for minor epidemics the probability profiles change considerably according to the stage of selection.

This model complements other disease models that have investigated the interaction between host genotype and disease epidemiology. For example, the nonlinear type responses similar to those seen in this study have also been observed in models of selection for resistance to nematode parasites (Bishop and Stear, 1997). The responses to selection for reduced fecal egg count were predicted to be up to twice that predicted by quantitative genetic theory, due to the altered disease epidemiology. The dynamics of scrapie in a sheep flock have been modeled by Stringer et al. (1998), in whose work susceptibility was modeled as being controlled by partially dominant allele, *r*. In this model there were three genotypes, *rr*, *rR*, and *RR*, which were fully susceptible, partially susceptible, and resistant, respectively. The model predicted that during a scrapie epidemic, the susceptible allele will decline in frequency due to natural selection, but that the epidemic will die out before the frequency has reached zero. Their finding is in agreement with our result that the probability of an epidemic reaches zero before the gene introgression process is complete.

When modeling disease transmission, it is critically important to define the situations under which the models apply. In this paper a sporadic viral disease was modeled, and consequences of selection can be described in terms of probability profiles. The source of infection is unknown and cannot be modeled. For diseases that cause widespread predictable epidemics, and there is a measurable environmental reservoir of infection, it is necessary to include this reservoir of infection as a parameter in the model. This requirement is especially applicable to diseases such as nematode infections in sheep and *E. coli* infections in pigs, for which the host genotype for resistance may actually influence the extent of the reservoir of infection. For diseases such as trypanosomiasis, for which the environmental reservoir of infection is essentially infinite, it is not appropriate to attempt to quantify either the probability of an epidemic or the degree of environmental challenge, other than as present or absent. In this situation, disease models would more appropriately look at the interactions between resistance and productivity and how these change with selection (van der Waaij et al., 2000).

In summary, these models provide a tool for animal breeders, allowing decisions to be made as to when selection for disease resistance is worthwhile. The results in this paper confirm and build on those presented by MacKenzie and Bishop (1999), who demonstrated the nonlinear responses to selection in terms of the proportions of animals infected during major epidemics, and the proportion of resistant animals necessary to protect the population from major epidemics. MacKenzie and Bishop (1999) also showed that, for a highly infectious disease (a large R_0), selection without the aid of major resistance genes is unlikely to provide benefits in the short, or even medium, term. Thus, the effort required in investigating the genetic contribution to resistance for particular diseases may be too great, unless there is evidence that there is a strong genetic component to resistance, for example, a major gene. In the event of such information becoming available, however, these models provide a necessary tool for investigating the costs, benefits, and risks associated with a particular pathogen and deciding then whether or not to proceed with a breeding program.

Implications

This article has important implications for the animal production industry. The model developed allows the effect of selection for resistance to microparasitic infection to be quantified prior to implementing a breeding program. Selection will reduce the probability of an epidemic and the severity of epidemics, should they occur. Furthermore, it is not necessary that all the animals on the farm be resistant to the disease for the farm to be free from epidemics. If the pathogen is highly infectious then it would be necessary to identify individual genes with large effects on resistance if progress is to be made in a reasonable time-scale. The model allows animal breeders to make informed decisions about what action is appropriate for specific pathogens.

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